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Improvement of physical activity after endobronchial valve treatment in emphysema patients

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ABSTRACT

Rationale: Bronchoscopic lung volume reduction using endobronchial valves is a promising treatment for severe emphysema patients without collateral ventilation. Physical activity is an important contributing factor for the autonomy, morbidity and mortality of these patients.
Objective: We investigated the impact of endobronchial valve treatment on physical activity in severe emphysema patients.
Methods: Physical activity was measured for 7 days by a triaxial accelerometer at baseline and 6 months follow-up after EBV treatment, and compared with standard medical care in a randomized controlled trial.
Results: Forty-three patients (77%female, age 59 ± 9years, FEV_1 30 ± 7%pred, steps 3563 ± 2213per/day) wore the accelerometer and were included in the analysis. Nineteen patients received EBV treatment and 24 standard medical care. At baseline, physical activity level was comparable between groups. After 6 months, the endobronchial valve group significantly improved compared to the controls in steps/day (+1252vs−148) and locomotion time (+17vs−2 min/day). Change in sit duration (0vs + 27 min/day) did not significantly differ.
Conclusions: Physical activity significantly improved after endobronchial valve treatment in severe emphysema patients. This improvement was without any specific encouragement on physical activity.
Clinical trial number: Dutch trial register: NTR2876.

1. Introduction

We recently showed that bronchoscopic lung volume reduction using endobronchical valves (EBV) is a promising treatment modality targeting lung hyperinflation for patients with severe emphysema [1]. The results of this randomized controlled trial showed that EBV treatment significantly improved pulmonary function, exercise capacity and quality of life after 6 months in COPD patients characterized by emphysema and the absence of interlobar collateral ventilation [1].

Potentially, the decrease in lung hyperinflation after EBV treatment could reduce dyspnea during exertion and consequently improve the functional capacity of the body. As dynamic and static lung hyperinflation are independent predictors of daily physical activity, especially in patients with advanced COPD [2,3], EBV treatment could potentially improve the patient's physical activity level. A higher physical activity level in these patients may improve the patient's exercise capacity and lead to restoration of social participation and a more independent lifestyle. Contrary, in a pilot study we demonstrated that physical activity did not significantly improve after bronchoscopic lung volume reduction treatment [4]. However, this uncontrolled study had a small sample size and investigated the bronchoscopic lung volume reduction treatment with coils instead of endobronchial valves. To our knowledge, the effect of bronchoscopic lung volume reduction using endobronchial valves on daily physical activity was not investigated before.

Our aim was to investigate whether daily physical activity in patients with severe emphysema increases after a bronchoscopic lung volume reduction treatment using endobronchial valves.

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2. Methods

2.1. Study population and study design

A randomized controlled crossover trial investigating the EBV treatment was performed in the University Medical Center Groningen in the Netherlands between June 2011 and November 2014 (STELVIO trial- Dutch trial register: NTR2876 [1]). Patients with emphysema and a visually determinable treatment target on the HRCT and proven absence of collateral ventilation between the target lobe and adjacent lobe were included. The complete list of in- and exclusion criteria can be found in Table E1 in the online supplement. In total 68 patients were randomized, of which 34 patients received EBV treatment ('EBV group'), whereas 34 patients received standard medical care ('control group'). After 6 months, the control group also received the EBV treatment ('crossover'). During the study, physical activity was measured by an accelerometer for 7 days at baseline and for 7 days after 6 months follow up (post randomization and post crossover). The study was approved by the ethics committee of the University Medical Center Groningen, and all patients provided informed consent.

2.2. Measurements

All measurements were performed at baseline and after 6 months follow-up (post randomization and post crossover). *Physical activity* was measured by a triaxial accelerometer (DynaPort, McRoberts). The accelerometer was worn around the waist at the lower back. This accelerometer is a highly validated instrument for evaluating physical activity in patients with COPD [5,6]. Patients were instructed to wear the accelerometer for 7 days, day and night, except during showering and swimming. *Lung function* Spirometry and bodyplethysmography were performed by blinded assessors (Jaeger MasterScreen™, CareFusion, Germany) according to the ATS/ERS guidelines [7–9]. *Exercise capacity* was measured by a 6-min walk distance (6MWD) test according to the ATS guidelines [10]. *Quality of life* was measured by the St. George's Respiratory Questionnaire [11]. *Dyspnea severity* was measured by the modified Medical Research Council (mMRC) scale [12].

2.3. Statistical analyses

Patients were included in the analyses if they had worn the accelerometer for at least 4 full days per assessment, in accordance with literature [13]. A day was considered a valid measurement day if the device was worn for at least 94% of the day [14]. When patients did not want to wear the accelerometer during the night, this time was recorded as lying. Six patients did not want to wear the accelerometer during the night and in total for 10 nights the time not worn was recorded as lying. Furthermore, to be included in the analyses the patient had to wear the accelerometer for at least 2 times; at baseline and after 6 months follow-up.

Differences between EBV group and control group were tested with an independent-samples *t*-test. Baseline and 6 months follow up measurements were compared with a paired-samples *t*-test or Wilcoxon signed-rank test. Pearson correlation coefficients were calculated to test univariate associations between physical activity parameters and other clinical parameters. P-values below 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 22.

3. Results

3.1. Participants

Characteristics of the 43 patients who had evaluable accelerometer data are shown in Table 1 and the flow of patients through the study is shown in Fig. 1. Of these 43 patients, 19 were treated with the EBV treatment and 24 patients received standard medical care. No significant differences in clinical characteristics or physical activity parameters were found between the EBV group and control group at baseline. After crossover of the control group, 18 patients also wore the accelerometer 6 months after crossover, leading to 37 patients with evaluable 6 months post EBV treatment data.

3.2. EBV treatment ($n = 19$) compared to controls ($n = 24$)

The differences between the EBV group and control group in change in physical activity and other clinical parameters between baseline and 6 months follow up are shown in Table 2 and Fig. 2. The EBV group significantly improved compared to the control group in mean steps per day (+1252 vs −148), locomotion duration (+17 vs −2 min per day) and locomotion intensity (+4.6 vs −1.5% change compared to baseline). The change in sitting duration (0 vs + 27 min per day) and inactivity duration (−16 vs + 6 min per day) did not differ significantly between groups. Furthermore, the EBV group significantly improved in spirometry results (FEV_1 and FVC), static hyperinflation (RV), dyspnea severity, quality of life and exercise capacity compared to the control group (Table 2).

3.3. EBV treatment including crossover ($n = 37$)

The changes in physical activity and other parameters between baseline and 6 months follow up including the crossover patients are shown in Table 3. The individual patient data of the change in steps per day is shown in Fig. 3. After EBV treatment patients significantly improved compared to baseline in steps per day (mean + 1133, 95%CI 711–1556), locomotion duration (mean + 16, 95%CI 9.3–21.9 min/day) and locomotion intensity (+3.1% change compared to baseline). Sitting duration (mean −10.5, 95%CI −36.5; 15.6 min/day) and inactivity duration (mean −16.2, 95%CI −39.6; 7.3 min/day) did not significantly change 6 months after EBV treatment.

3.4. Association between physical activity and other clinical variables

The univariate associations between physical activity parameters and other clinical variables are shown in Table E2 in the online supplement.

In the population including the EBV group and crossover EBV group (n = 37) change in steps per day was not significantly associated with change in other clinical variables.

4. Discussion

To our knowledge, this was the first study that measured physical activity before and after EBV treatment in patients with severe COPD. Our results showed that physical activity significantly improved 6 months after EBV treatment with a difference in improvement in physical activity by 1340 steps per day between the EBV group and the control group.

A recent paper of Waschki et al. showed that patients in GOLD stage III to IV loose approximately 450 steps per year [15]. Comparing our results with this study means that the difference in improvement in steps per day of 1340 in our study corresponds to

Table 1
Patient characteristics.

	EBV treatment group (n = 19)	Control group (n = 24)
Male, n (%)	6 (32%)	4 (17%)
Age, years	59 ± 10	59 ± 7.4
BMI, kg/m^2	25.7 ± 4.6	24.1 ± 4.0
FEV_1, %pred	31.7 ± 7.8	29.5 ± 7.1
FVC, %pred	79.7 ± 13.2	78.4 ± 19.1
RV, %pred	210 ± 28	219 ± 33
RV/TLC, %	57.9 ± 8.0	60.8 ± 8.1
SO2, %	94.6 (90–97.9)	94.1 (88.2–96.8)
mMRC, score	2.4 ± 0.7	2.7 ± 0.6
SGRQ, total score	52.5 ± 11.9	59.4 ± 12.6
EQ5D, vas score	52.5 ± 15.7	52.4 ± 16.3
CCQ, total score	2.6 ± 0.7	2.7 ± 0.6
6MWD, meter	366 ± 82	388 ± 74
Steps, mean per day	3483 (714–11352)	2982 (964–7808)
Walk intensity, g	0.173 ± 0.029	0.169 ± 0.023
Locomotion duration, %/day	4.7 ± 2.5	4.5 ± 2.3
Sit duration, %/day	40.3 ± 9.9	38.9 ± 8.3
Inactivity duration, % day	83.3 ± 5.9	82.8 ± 5.9
Physiotherapist training ≥ 2/week, n (%)	15 (79%)	20 (83%)
Pulmonary rehabilitation <24 months, n (%)	9 (47%)	13 (54%)

Data are presented as n (%), mean ± sd or median (range).
BMI: Body mass index; FEV_1: Forced Expiratory Volume in 1 s, FVC: Forced vital capacity, RV: Residual volume, TLC: Total lung capacity, SO2: Oxygen saturation, mMRC: medical Modified Research Council, SGRQ: St. George's Respiratory Questionnaire, EQ5D: EuroQol 5D questionnaire; CCQ: Clinical COPD Questionnaire, 6MWD: 6-min walk distance.

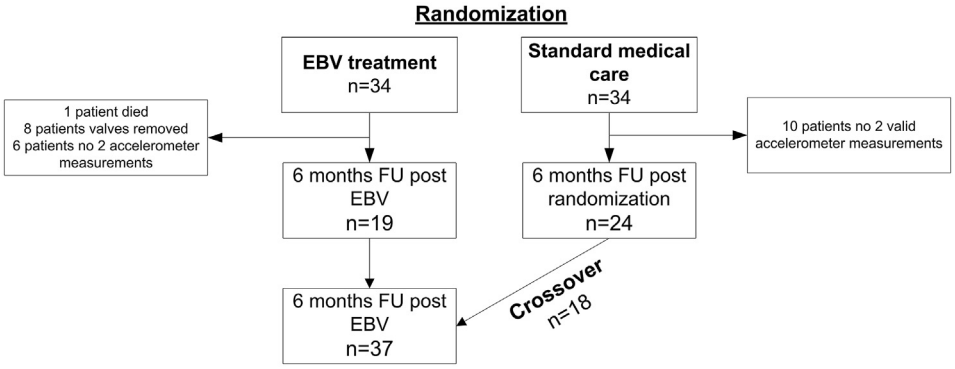

Fig. 1. Flowchart of participant flow through the study.

Table 2
Difference between EBV treatment group and control group in change in physical activity and other clinical characteristics at 6 months FU.

	EBV treatment (n = 19) group		Control group (n = 24)		Between group	
	Δ absolute change	Δ % change	Δ absolute change	Δ % change	Difference	p-value
Steps, mean per day	1252 ± 1468	57.1 ± 73.3	−148 ± 862	−1.2 ± 18.8	1340 ± 380	**0.001**
Locomotion duration, %/day	1.15 ± 1.46	36.4 ± 49.7	−0.13 ± 0.93	−1.6 ± 16.6	1.28 ± 0.37	**0.001**
Walk intensity, g	0.0067 ± 0.0141	4.6 ± 8.4	−0.0028 ± 0.008	−1.5 ± 4.6	0.00948 ± 0.0036	**0.014**
Sit duration, %/day	0.01 ± 6.1	1.44 ± 19.0	1.88 ± 3.0	5.22 ± 8.2	−1.86 ± 1.52	0.230
Inactivity duration, min day	−1.1 ± 3.2	−1.3 ± 3.9	0.39 ± 3.0	0.62 ± 3.65	−1.49 ± 0.95	0.126
FEV_1, ml	173 ± 226	25.1 ± 28.5	22.5 ± 95.8	3.2 ± 10.9	150 ± 51	**0.005**
FVC, ml	472 ± 572	21.5 ± 27.7	69.2 ± 365.0	3.6 ± 14.4	403 ± 144	**0.008**
RV, ml	−880 ± 517	−20.1 ± 11.4	−40.8 ± 265.6	−0.5 ± 6.0	−838 ± 122	**<0.001**
mMRC, score	−0.58 ± 0.69	−21.9 ± 24.9	−0.04 ± 0.46	−0.69 ± 17.4	−0.54 ± 0.18	**0.007**
SGRQ, total score	−15.7 ± 16.3	−27.6 ± 28.0	−3.0 ± 9.1	−3.7 ± 13.7	−12.7 ± 4.2	**0.005**
6MWD, meter	84.5 ± 62.1	26.4 ± 22.0	−19.5 ± 35.4	−5.1 ± 10.4	104.0 ± 16.3	**<0.001**

Data are presented as mean ± sd. Δ absolute change: absolute change between 6 months follow up and baseline, Δ % change: relative change between 6 months follow up and baseline, g: average body acceleration. Difference between groups in Δ absolute change were tested with an independent-samples *t*-test. Significant values ($p < 0.05$) are depicted in bold. FEV_1: Forced Expiratory Volume in 1 s, FVC: Forced vital capacity, RV: Residual volume, mMRC: medical Modified Research Council, SGRQ: St. George's Respiratory Questionnaire, 6MWD: 6-min walk distance.

the amount of steps that COPD patients loose in 3 year. Furthermore, the improvement exceeds the recently established minimal important difference (MID) for steps per day of 600–1100 [16].

In contrast to the pilot study with coils [4], the current study did demonstrate significant improvements in daily physical activity after treatment with endobronchial valves. The pilot study

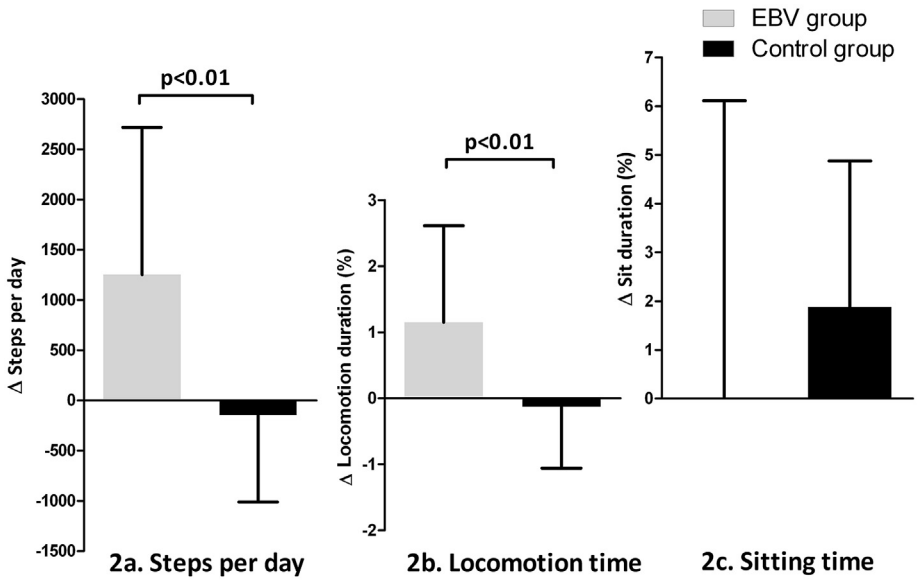

Fig. 2. Change between baseline and 6 months follow up in steps per day, locomotion time and sitting time in EBV group and the control group. Bars represent means and standard deviations.

Table 3
Change in clinical characteristics at 6 months after EBV treatment (n = 37).

	Baseline	6-month follow up	p-value	Δ relative change
Steps, mean per day	3456 ± 2216	4589 ± 2493	<**0.001**	47.5 ± 56.9%
Locomotion duration, %/day	4.6 ± 2.5	5.6 ± 2.6	<**0.001**	34.4 ± 41.8%
Walk intensity, g	0.170 ± 0.026	0.174 ± 0.025	**0.040**	3.1 ± 7.6%
Sitting duration, %/day	40.9 ± 9.2	40.2 ± 9.8	0.421	−1.1 ± 15.7%
Inactivity duration, min day	83.1 ± 5.4	82.0 ± 7.1	0.171	−1.3 ± 6.0%
FEV_1, %pred	31.1 ± 7.8	38.4 ± 8.8	<**0.001**	25.6 ± 21.3%
FVC, %pred	80 (54–110)	96 (57–135)	<**0.001***	17.6 (−15–58)%
RV, %pred	216 (161–273)	170 (108–251)	<**0.001***	−18.0 (−44.7–5.48)%
mMRC, score	2.5 ± 0.65	2.0 ± 0.65	<**0.001**	−16.9 ± 21.9%
SGRQ, total score	54.2 ± 10.3	40.1 ± 15.8	<**0.001**	−24.9 ± 26.6%
6MWD, meter	366 ± 82	433 ± 74	<**0.001**	21.3 ± 18.6%

Data are presented as mean ± sd or median (range). Differences between baseline and 6 months follow up were tested with a paired-samples *t*-test or *Wilcoxon signed rank test. Significant values ($p < 0.05$) are depicted in bold.
Δ relative change: relative (%) change between baseline and 6 months follow up.
FEV_1: forced expiratory volume in 1 s, FVC: forced vital capacity, RV: residual volume, mMRC: modified Medical Research council scale, SGRQ: St. George's respiratory questionnaire, 6MWD: 6-min walk distance.

investigating the coil treatment was uncontrolled and had a small sample size (n = 14) and the number of steps only increased on average 400 steps per day 6 months after the treatment. The reason for this difference could be a less effective treatment as also the changes in other clinical parameters, like lung hyperinflation and exercise capacity were less pronounced after treatment with coils. Furthermore, the patients in the study who were treated with coils were one of the first patients ever treated and a best-responder profile for this treatment is not defined yet. Currently, there is more knowledge on the group of patients that will potentially benefit of the treatment with valves than with the treatment with coils.

If we compare our EBV treatment effects on physical activity with those of pharmacological treatment or pulmonary rehabilitation we must keep in mind that we selected very severe emphysema patients, yet fit enough to undergo EBV treatment. Four randomized controlled trials investigating a long-acting bronchodilator showed inconsistent results regarding physical activity in patients with mainly moderate COPD. Two studies did not find a significant improvement in physical activity after 3 weeks or 24 weeks of treatment in contrast to two studies with 3 week follow up demonstrating significant improvement in number of steps (722 steps per day) and moderate intensity daily activity (10.1 min per day) compared to a placebo group [17–20]. The results of the effect of pulmonary rehabilitation on physical activity is inconsistent and a review concluded that exercise training (not only rehabilitation) has a small but significant effect on physical activity [21,22].

Our results showed that physical activity significantly improved after EBV treatment in the short term up to 6 months after treatment and it would be interesting to also investigate the effects on the longer term. To maintain the effects in the long term, or even further improve them, it could be useful to provide a physical activity enhancement program after the EBV treatment, for example by following a pulmonary rehabilitation program. Furthermore, physical activity counselling programs focusing on physical activity in daily life showed promising results [23,24] and these programs could also be useful to sustain the effects in the long term.

In the total group receiving EBV treatment (including crossover patients) we found no significant associations between changes in physical activity and changes in lung function, exercise capacity or quality of life. Therefore, a larger decrease in hyperinflation is not

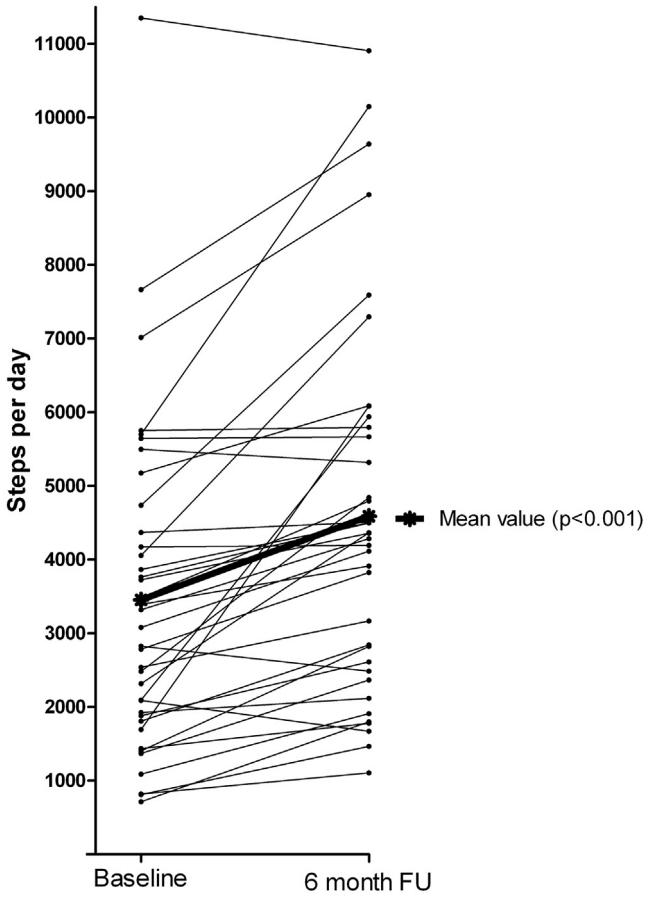

Fig. 3. Individual patient data at baseline and 6 month follow up for steps per day. For the control group, baseline was 6 months after randomization.

proportionally associated with a larger improvement in physical activity. Probably other factors play a role as well in the size of the improvement in physical activity after the EBV treatment. These factors could be psychological factors such as motivation or self-efficacy and/or chronic deconditioning, atrophic muscles or the patient's history of physical activity. A physical activity enhancement program after the EBV treatment could target these factors as well to increase the physical activity level even more.

We found that sitting time decreased by 11 min per day and the EBV group did not significantly differ in the change in sitting time compared to the control group. Sitting time has been associated with an increased risk of mortality, even independent of leisure time physical activity [25]. Furthermore, sedentary time has shown to be an independent risk factor for several health outcomes like cardiovascular risk factors, independently of physical activity [26]. Breaking-up sitting time could be beneficial, as it was shown to be beneficially associated with metabolic risk variables and physical function [27–29]. Therefore, it could be important to also pay attention to break-up sitting time besides enhancing physical activity after the EBV treatment.

A limitation of our study was the relative small sample size, but we did have a control group which strengthens our findings. Another limitation is the high number of patients who were lost to follow up. However, there were no differences in baseline physical activity parameters between the patients who were lost to follow up and the patients included in the analyses (data not shown). A large trial, ideally sham-controlled, would be useful to confirm our results. Furthermore, we only measured physical activity 6 months after the treatment and consequently physical activity was measured during 2 different seasons, which could strongly influence physical activity. On the other hand, both EBV and control group patients were measured throughout the year. Ideally, physical activity should be measured multiple times throughout 1 year including all seasons. Finally, it should be acknowledged that a large proportion of the study population were women.

The primary outcomes of most of the randomized controlled trials investigating a lung volume reduction treatment modality in patients with severe COPD are pulmonary function or exercise capacity (*e.g.* NETT [30], VENT [31], RENEW (NCT01608490) and LIBERATE (NCT01796392)). Such outcome variables are important to understand and prove the mechanistic benefits of lung volume reduction treatment, but ultimately we need patient-centered outcomes to show that the treatment is also beneficial in the perception of the patient. In this perception the RESET trial demonstrated that quality of life improved after the coil treatment [32]. Another important patient-centered outcome would be physical activity which has been shown to be associated with decreased dyspnea severity, improved muscle function, improved quality of life and decreased risk of mortality in patients with COPD [33–36]. Furthermore, physical activity is an important prerequisite for an independent lifestyle and social participation. Therefore, we put forward that physical activity should be considered as an important clinical outcome variable in clinical trials investigating treatments for severe COPD.

In conclusion, we found that daily physical activity significantly improved 6 months after bronchoscopic lung volume reduction treatment using one-way endobronchial valves. This improvement was without any specific encouragement on physical activity. Therefore, it would be very interesting to investigate the potential additional effect when combining the EBV treatment with a physical activity counselling program or pulmonary rehabilitation program.

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Conflict of interest statement

NHT and JH have no conflicts of interest, **KK** received travel grants and a speakers fee from PulmonX, **DJS** is a physician advisor to PulmonX, received travel grants and lecture fees for educational and scientific meetings from PulmonX and participates in other clinical trials funded by PulmonX. All authors had complete access to the data, reviewed and approved the manuscript. PulmonX was not involved at any stage during the trial.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.06.009.

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